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**Anterior Cruciate Ligament and Meniscal injuries increase the risk
of primary total knee replacement for osteoarthritis: a matched
case-control study using the Clinical Practice Research Datalink
(CPRD)**

T Khan¹, A Alvand², D Prieto-Alhambra², D Culliford³, A Judge², WF Jackson²,
BE Scammell¹, N Arden² & AJ Price²

¹ Department of Orthopaedics, Trauma & Sports Medicine, University of Nottingham.

² Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences,
University of Oxford.

³ University of Southampton

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Abstract

Introduction

There is an established association between anterior cruciate ligament (ACL) and meniscal injuries and an increased risk of knee osteoarthritis (OA). However, there is limited evidence of the progression to end-stage OA. The aim of this study was to investigate whether ACL injury (ACLi) or meniscal injury increase the risk of developing end-stage OA requiring Total Knee Replacement (TKR).

Methods

A matched case-control study of all TKRs performed in the UK between January 1990 and July 2011 and recorded in the Clinical Practice Research Datalink (CPRD) was undertaken. The CPRD contains longitudinal data on approximately 3.6 million patients from over 480 general practices. Two controls (control group) were selected for each case of TKR (case group), matched based on age, sex and general practice. Individuals with inflammatory arthritis were excluded. The odds of having TKR for individuals with a CPRD-recorded diagnosis of ACLi were compared with those without ACLi using chi-squared analysis and conditional logistic regression, after adjustment for body mass index, previous knee fracture, and meniscal injury. Similarly, the adjusted odds of TKR in individuals with a recorded meniscal injury compared to those without was calculated (adjusted for ACLi, body mass index and history of previous fracture around the knee).

Results

A total 49,723 CPRD participants had a TKR recorded between 1990 and 2011 (104,353 controls). 153 (0.31%) cases had a previous history of ACLi compared to 41 (0.04%) controls ($p<0.05$). The adjusted odds ratio of TKR after ACLi was 6.96 (95% CI 4.73-10.31, $p<0.001$). 4217 (8.48%) individuals in the TKR group had a recorded meniscal injury compared to 669 (0.64%) controls. The adjusted odds ratio of TKR after meniscal injury was 15.24 (95% CI 13.88-16.69, $p<0.001$).

Conclusions

This study demonstrates that ACL injury is associated with a 7-fold excess risk of TKR resulting from end-stage knee OA. Furthermore, meniscal injury is

independently associated with a 15-fold increase in risk of TKR for OA. Further work is needed to investigate the potential effect of ACL reconstruction or meniscal surgery to reverse or minimise this association.

Introduction

The anterior cruciate ligament (ACL) and the menisci are key functional structures in the knee and are both frequently injured. Meniscal tears are the most common knee injury, with an estimated prevalence between 2.5 and 4 times higher than ACL rupture [1-4]. The estimated annual incidence of ACL injury has been reported as high as 0.8 per 1000 population [5]. The menisci are key structures in the distribution of load across the joint and the ACL is one of the principle stabilizing ligaments that couples tibial and femoral movement [6-8].

There is convincing evidence that both injuries are associated with an increased risk for patients of developing knee osteoarthritis (OA) at long-term follow-up. ACL injury predisposes the knee to radiographic OA at a mean follow-up of over 10 years when comparing injured knees with uninjured contralateral knees [9] [10]. Lohmander et al. reported that approximately 50% of individuals who had undergone meniscectomy 10 to 20 years previously, demonstrated signs of radiographic OA [2].

Whilst the risk of developing OA has been established, there is limited long-term evidence that ACL or meniscal injury are associated with progression to end-stage knee OA and the eventual need for joint replacement. In fact, few studies reporting the functional and symptomatic outcomes of ACL injury include more than 10-years follow-up data [11]. In a similar manner the quantitative effect of meniscal injury on the risk of end-stage osteoarthritis is not known.

Total Knee Replacement (TKR) is an effective treatment for advanced painful osteoarthritis of the knee [12], with more than 670 000 performed in the US alone in 2012 [13]. As pain and extent of radiographic OA are key variables in the decision to perform a TKR [14-16], joint replacement acts as a useful surrogate for end-stage OA and has been used in pharmacological studies as a marker of severe osteoarthritic disease [17, 18]. Within the UK Clinical Practice Research Datalink (CPRD), ACL, meniscal injury, and joint replacement are all coded which allows their interrelationship to be investigated.

The purpose of this case-control study was to compare the risk of undergoing a TKR for knee OA in individuals with a history of ACL rupture or meniscal injury with the risk for individuals without a prior ACL rupture or meniscal injury.

Methods

Study Design & Data Source

A matched case-control study of all primary TKRs performed between January 1991 and July 2011 and recorded in the Clinical Practice Research Datalink (CPRD) was undertaken. The CPRD is a large computerized primary care database containing longitudinal data on approximately 3.6 million patients (roughly 6% of the UK population) registered at 480 general practices in the UK. It is generally considered that individuals recorded in the CPRD are representative of the wider UK population in terms of age, sex and socioeconomic status [19]. General practices record patient demographics, consultations, diagnoses, specialist referrals, hospital treatment, prescriptions and test results. 'Read codes' are used to enter clinical information, which are standard clinical terminologies used within UK primary care. The data quality is regulated by the Medicines and Healthcare Products Regulatory Authority (MHRA).

Participants

All patients in the CPRD with a diagnosis code for TKR from January 1990 until July 2011 were identified. Previously validated Read codes were used to identify primary TKRs [19-21]. Individuals with a code for primary TKR were included in the analysis if they were aged 18 years and older at the time of TKR and those with a recorded diagnosis of inflammatory arthritis were excluded from the study.

Each case of primary TKR recorded in the CPRD (case group) and fulfilling the inclusion criteria was matched to two controls (control group). The criteria for matching cases to controls was on the basis of age, sex and GP practice, which served as a proxy for socioeconomic status via deprivation score in terms of the practice location. Controls were selected randomly from individuals in the CPRD fulfilling the matching criteria for each case subject.

The CPRD medical dictionary was used to search for Read codes for ACL injury. Read codes were selected which referred to ACL and meniscal injuries by the first

author (TK) and these were verified by co-investigators (2 Orthopaedic Surgeons – AJP, AA and 1 statistician - DC).

Ethical approval was obtained prior to commencement of this study from the Independent Scientific Advisory Committee of the Clinical Practice Research Datalink.

Data Management and Statistical Analysis

Data management and statistical analysis was performed using STATA SE version 12. Demographics of the case and control groups were compared using chi-squared test for categorical variables and t-test for continuous variables. The odds of having a TKR for individuals with ACL injury recorded as an event were compared with those without ACL injury using chi-squared analysis followed by conditional logistic regression. The results were adjusted for body mass index (BMI), previous fractures around the knee, and history of meniscal injury. Multiple imputation methods were used in order to account for missing body mass index information [22, 23].

The conditional logistic regression model was also used to determine the unadjusted and adjusted odds (adjusted for previous fractures around the knee, a history of ACL injury and body mass index) of undergoing TKR for individuals with meniscal injury recorded as an event compared to those without a documented meniscal injury.

To establish the odds of TKR for individuals with both a recorded ACL injury and a meniscal injury compared to those with a history of ACL injury only, an interaction term was added to the conditional logistic regression model.

We hypothesized that entry of individuals with ACL injury or meniscal injury onto the CPRD might have become more robust in later years, due to an increased access to MRI scans, which may impact the comparative odds. Hence, we conducted a sensitivity analysis where TKR cases performed before January 1st 2000 and matched controls were excluded.

Results

Within the study period, 52,530 patients in the CPRD had a primary TKR for any indication and were matched to 105,060 controls. After excluding patients with a recorded diagnosis of inflammatory arthritis, there were 49,723 individuals with TKR and 104,353 controls.

The mean age of individuals in the case group was 70.4 (SD 9.5) and 57.5% of them were females. This was similar for the controls due to matching. The BMI was higher for the TKR group. The clinical characteristics of the two groups are summarized in Table 1.

153/49,723 (0.31%) TKR cases had sustained an ACL injury compared to 41/104,353 (0.04%) controls ($p < 0.001$, chi-squared test). The unadjusted odds ratio of undergoing TKR, within the 20-year period, in individuals with a recorded ACL injury compared to individuals with no history of ACL injury was 8.00 (95% CI 5.61-11.42). Following multivariable adjustment, the adjusted odds ratio was 6.96 (95% CI 4.73-10.31). The unadjusted and adjusted odds ratios (adjusted for BMI, ACL injury and fractures around the knee) for TKR in individuals with a recorded meniscal injury versus those without were 15.31 (95% CI 13.99-16.75) and 15.24 (95% CI 13.88-16.69) respectively. Table 2 summarizes the characteristics of TKR patients in individuals with a previous ACL injury and those without.

39 individuals in the case group had a recorded diagnosis of both ACL injury and meniscal injury, compared with 3 individuals in the control group. The adjusted odds ratio for TKR in individuals with both a recorded ACL and meniscal injury compared with those with only an ACL injury recorded was 4.19 (95% CI 1.05 – 16.66).

In a sensitivity analysis excluding patients who underwent TKR before 1st January 2000, there were 42,722 cases and 88,929 controls available for analysis. The unadjusted odds ratio of TKR in individuals with an ACL injury versus those without was 7.74 (95% CI 5.42-11.06). After adjusting for body mass index, previous fractures around the knee, and a history of meniscal injury, the odds ratio was 6.81 (95% CI 4.59 – 10.11). For meniscal injury, the unadjusted odds of TKR was 15.46

(95% CI 14.06–17.00). After adjustment for BMI, history of ACL injury and previous fractures around the knee, the odds ratio was 15.38 (95% CI 13.96– 16.96)

Discussion

This matched case-control study demonstrates that ACL and meniscal injuries are both significant independent risk factors for the development of end-stage osteoarthritis requiring TKR, with an estimated 7 and 15-fold increased odds respectively. This is the first epidemiological study to quantify this important link based on 20-year longitudinal data.

The vast majority of previous studies investigating the link between ACL injury and osteoarthritis use radiological changes as the primary outcome measure. Neuman [24] reported outcomes in 100 individuals with acute ACL injury at 15 years follow-up. They found signs of radiographic OA in 16% of the 79 patients who underwent imaging at follow-up. The incidence of knee OA after ACL injury reported by Neuman [24] is significantly lower than that reported in other studies [25-28]. However, regardless of the overall incidence, from these series it is difficult to determine the influence of ACL rupture on the long-term risk of developing osteoarthritis based on relatively small cohort studies without a control group of uninjured patients. Ajuied and colleagues, in a meta-analysis, reported a relative risk of 3.84 for developing moderate or severe radiologic osteoarthritis (Kellgren and Lawrence grade III or IV) at a mean of 10 years follow-up in ACL injured individuals compared to those with no history of ACL injury [10]. Due to the case-control design of the present study, relative risk cannot be calculated directly, but the odds ratios can be used as an estimate of the risk. Hence, in comparison with Ajuied's meta-analysis, although similar, the overall probability of OA appears higher in the present study. There are several possible explanations for this. Firstly, the follow-up period was substantially longer in the present study, which is likely to contribute to the difference. Secondly, the meta-analysis assessed studies comparing radiographic changes in the ACL injured with the contralateral uninjured knee within individuals. In contrast, the present study compared odds in individuals with a recorded diagnosis of ACL injury to those without. The present study is therefore likely to be a closer estimate of the probability of end-stage OA attributable to ACL injury within the population.

Studies reporting the long-term outcomes of surgically treated meniscal injuries have demonstrated a similar association to the present study with an increased risk of OA. In a recent systematic review of osteoarthritis after total or partial meniscectomy, Papalia et al, reported an overall mean prevalence of osteoarthritis of 53% on the operated knee, compared to a range of 0-44% in the contralateral non-operated knee at a mean follow-up of 13.3 years [29]. Furthermore, early structural changes following meniscal injury and meniscectomy which result in an increased risk of developing radiographic OA, have been reported [30, 31]. Roemer, using data from the Osteoarthritis Initiative, demonstrated that the presence of MRI-detected meniscal damage 2 years prior to incident radiographic OA, increased the risk of incident radiographic OA. The OR for the medial meniscus was 1.83 (95% CI 1.17-2.89) and 1.56 (95% CI 0.85-2.84) for lateral meniscus [30]. In the present study we have demonstrated a previously unreported significant association between meniscal injury and end-stage knee osteoarthritis requiring TKR. It is likely that some, but not all, of the individuals identified in the case and control groups with a prior diagnosis of meniscal injury, would have received surgical treatment. Although, we cannot comment on whether or not the method of treatment of acute meniscal injury influence the risk of developing severe osteoarthritis, this study provides important insight into the natural history of this condition.

The present study has some limitations. Firstly, as in any case-control study, there is the possibility of recall bias, although this is minimized in studies based on electronic medical records, where both the outcome (TKR) and the previous exposure (here ACLi and meniscal injury) were coded at the time when they happened. Nevertheless, the risk of more accurate recording of orthopaedic surgery amongst patients diagnosed with an ACLi or meniscal injury, as well as an increased provision of TKR for patients previously in contact with orthopaedic surgery (due to ACLi or meniscal injury) leads to similar issues (i.e. Berkson's bias [32]). Secondly, we were limited by the recording of ACL and meniscal injuries in the CPRD, and no individual validation of exposure or event have been undertaken. However, if such diagnoses were under-recorded, this is likely to affect both the case and control groups approximately equally and therefore should not significantly affect the calculated odds ratios. TKR coding in CPRD has been recently validated by our group with good accuracy when compared to hospital admission records [33, 34]. Thirdly, another limitation is that we

were not able to establish from the CPRD the laterality of neither the TKR nor ACL injuries for the individuals. Although this warrants some caution in interpreting the exact value of the calculated odds ratio, it is unlikely to alter the overall conclusions.

The case-control design of the study did not allow us to undertake an analysis of operative/non-operative management of ACL and meniscal injuries, which is perhaps an important potential confounder. With respect to ligament reconstruction, two previous population based cohort studies have addressed this question [35, 36]. A study based on records for cruciate ligament reconstruction (may include posterior cruciate ligament) procedures, reported a 7 times higher incidence of TKR after cruciate ligament reconstruction compared to a matched cohort of individuals from the general population [35]. Although an area of some debate, if it is assumed that ACL reconstruction does not protect against the risk of TKR in ACL injured patients [36], the results of the present study are not dissimilar to those reported by Leroux et al [35]. However, due to the difference in study design, direct comparisons are not possible. For meniscal surgery, Lohmander reviewed 41 studies and reported an overall estimated odds ratio of 10 for radiographic knee osteoarthritis 15 to 20 years after meniscectomy when compared to an age and sex matched group with no history of knee injury [2]. The authors did indicate in their review that the better designed cohort studies reported a much higher incidence of radiographic OA after meniscectomy, which would equate to a higher odds ratio compared to age and sex matched uninjured individuals.

It has been estimated that the lifetime risk of TKR for an individual aged 50 is as high as 10.8% for women and 8.1% for men [19]. Since, ACL and meniscal injuries are increasing in incidence [37, 38], and given the findings of this study, it is reasonable to assume that a significant number of TKRs performed are the sequelae of these injuries. It follows that the socioeconomic impact of ACL and meniscal injuries is substantial in both the short-term and long-term. Mather [39] estimated the life time burden of ACL injuries in the US to be between \$7.6 billion and \$17.7 billion depending on treatment strategy. Based on the US model, the same study suggested 25,000 to 30,000 TKRs per year are attributable to ACL injury [39]. The present study supports the claim that ACL injury contributes directly to the financial burden of end-stage osteoarthritis requiring knee arthroplasty. Therefore, strategies to prevent

knee injury including targeted training programs [40-42] as well treatment methods to avoid the onset and progression of osteoarthritis following these injuries are likely to reduce the TKR burden.

In conclusion, this study demonstrates a strong association between ACL and meniscal injuries and the risk of TKR later in life. Further work should focus on determining whether initial treatment of the meniscal and ACL injury has any effect in reducing the long-term risk of end-stage knee OA.

Figures and Tables

Table 1: Characteristics of CPRD-recorded cases of Total Knee Replacement with matched controls.

	Cases	Controls	P value
Total (n)	49,723	104,353	-
Age in years (SD)	70.3 (9.5)	70.1 (9.6)	-
Female n (%)	28,540 (57.4%)	60,662 (58.1)	-
BMI (SD)	28.68 (4.93)	25.83 (4.58)	P<0.001
Prior diagnosis of ACL injury	153 (0.31%)	41 (0.04%)	p<0.001
Prior diagnosis of meniscal injury	4217 (8.48%)	669 (0.64)	p<0.001
Prior fracture around the knee	11328 (22.78%)	17779 (17.04%)	P<0.001

Table 2: Characteristics of all CPRD-recorded patients with Total Knee Replacement by prior diagnosis of ACL injury.

	Previous ACL injury	No Previous ACL injury
Total (n)	153	49570
Mean age in years (SD)	57.3 (11.3)	70.4 (9.4)
Gender F:M	42 : 111	28498 : 21072
Mean BMI (SD)	28.04 (3.95)	28.69 (4.93)
Meniscal injury n (%)	39 (25.49)	4178 (8.4)
Fractures around the knee n (%)	0 (0)	32 (0.06)

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